

adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor or anti-sense to their respective mRNA; pharmaceutically and veterinarily acceptable salts of the oligo(s) or mixtures thereof; and a surfactant that may be operatively linked to the nucleic acid.

109. The composition of claim 108, wherein the oligo consists of up to about 10% A.

110. The composition of claim 109, wherein the oligo consists of up to about 5% A.

111. The composition of claim 110, wherein the oligo consists of up to about 3% A.

112. The composition of claim 111, wherein the oligo is A-free.

113. The composition of claim 108, wherein the oligo is anti-sense to the initiation codon of the mRNA, to the 5' or 3' intron-exon junctions or to sequences of the coding region comprising 2 or more G and/or C of the adenosine A<sub>1</sub> receptor gene.

114. The composition of claim 108, wherein the oligo is anti-sense to the initiation codon of the mRNA, to the 5' or 3' intron-exon junctions or to sequences of the coding region comprising 2 or more G and/or C of the adenosine A<sub>2a</sub>, A<sub>2b</sub> and/or A<sub>3</sub> receptors.

115. The composition of claim 108, wherein if the oligo contains adenosine (A), at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A<sub>2a</sub> receptor.

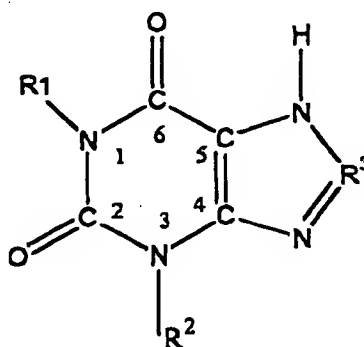
116. (Amended) The composition of claim 115, wherein substantially all As are substituted by a universal base (s) selected from heteroaromatic bases that bind to a thymidine base but either have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors, or heteroaromatic bases [which] that have no activity or have [an] agonist activity at the adenosine A<sub>2a</sub> receptor.

117. (Amended) The composition of claim 115, wherein the heteroaromatic bases are selected from pyrimidines or purines that may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH or branched or fused primary or secondary amino, alkyl,

alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, or arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary or tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl or heteroaryl.

118. The composition of claim 117, wherein the pyrimidines are substituted at a 1, 2, 3, and/or 4 position, and the purines are substituted at a 1, 2, 3, 4, 7 and/or 8 position.

119. The composition of claim 118, wherein the pyrimidines or purines are selected from theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline or xantine having the chemical formula



wherein R<sup>1</sup> and R<sup>2</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxymethoxy-aryl or mono or dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub> aryl.

120. The composition of claim 116, wherein the universal base is selected from 3 - nitropyrrole - 2' - deoxynucleoside, 5 - [nitro-indole] nitroindole, 2 - deoxyribosyl - (5 - nitroindole), 2 - deoxyribofuranosyl - ( 5 - nitroindole), 2' - deoxyinosine, 2' - deoxynebularine, 6H, 8H - 3, 4 - dihydropyrimido [4, 5 - c] oxazine - 7 - one or 2 - amino - 6 - methoxyaminopurine.

121. The composition of claim 108, wherein a methylated cytosine (<sup>m</sup>C) is

SERIAL NO: 08/093,972

PATENT

substituted for an unmethylated cytosine (C) in at least one CpG dinucleotide if present in the nucleic acid(s).

122. The composition of claim 108, wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotrithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

123. The composition of claim 122, wherein substantially all mononucleotides are linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotrithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty

acids.

124. The composition of claim 108, wherein the anti-sense oligo comprises about 7 to 60 mononucleotides.

125. (Twice Amended) The composition of claim 108, wherein the oligo comprises a sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 966 [1035], or

SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 966 [1035], wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotrithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA Sulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

126. The composition of claim 108, wherein the nucleic acid is linked to an agent that enhances cell internalization or up-take and/or a cell targeting agent.

127. The composition of claim 126, wherein the cell internalization or up take enhancing agent is a transferrin, a asialoglycoprotein or a streptavidin.

128. The composition of claim 126, wherein the cell targeting agent comprises a vector, and the nucleic acid is operatively linked to the vector.

129. The composition of claim 128, wherein the vector comprises a prokaryotic or eukaryotic vector.

130. The composition of claim 108, wherein the surfactant is selected from surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and

SERIAL NO: 08/093,972

PATENT

surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfaridic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, lamellar bodies, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene ethers, phenoxy polyethoxy alcohols, phosphatidyl choline esters and phosphatidyl ethers, palmitates, alcohols and tyloxapol, phospholipids, neutral lipids, fatty acids or surfactant-associated proteins or  $C_{22}H_{42}O_2$

131. (Twice Amended) The composition of claim 130, wherein the the surfactant is selected from polyoxy ethylene 23 lauryl ether (Brij 35<sup>®</sup>), t-octyl phenoxy polyethoxy ethanol (Triton X-100<sup>®</sup>), dipalmitoyl phosphatidyl choline (DPPC) and phosphatidyl glycerol (PG) (ALEC<sup>®</sup>), [colfoceryl-cetyl alcohol-tyloxapol or colfosceril palmitate, cetyl alcohol,] tyloxapol (Exosurf<sup>®</sup>), phospholipids, [neutral lipids,] fatty acids, surfactant-associated proteins (Survanta<sup>®</sup>) or  $C_{22}H_{42}O_2$  (Atovaquone<sup>®</sup>).

133. The composition of claim 108, wherein the carrier comprises a biologically acceptable carrier.

134. The composition of claim 108, wherein the carrier is a pharmaceutically or veterinarily acceptable carrier.

135. The composition of claim 134, wherein the carrier is selected from gaseous, liquid and solid carriers or mixtures thereof.

136. The composition of claim 108, further comprising an agent selected from therapeutic agents other than the nucleic acid(s), antioxidants, flavoring or coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, flavoring agents, propellants or preservatives.

137. (Twice Amended) The composition of claim 136, comprising

a pharmaceutically or veterinarily acceptable carrier,

the nucleic acid,

a surfactant, and

a therapeutic agent selected from adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor activity inhibiting agents other than the oligo(s), anti-arrhythmic agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, adenosine or agents exhibiting adenosine agonist activity, analgesics, diuretics, kidney activity maintenance or restoration agents or agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, acute respiratory distress syndrome (ARDS), ischemia, impeded and blocked respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD).

138. The composition of claim 136, wherein the RNA inactivating agent comprises an enzyme.

139. The composition of claim 138, wherein the enzyme comprises a ribozyme.

140. The composition of claim 108, further comprising a propellant.

141. The composition of claim 108, wherein the nucleic acid is present in an amount of about 0.01 to about 99.99 w/w of the composition.

143. The formulation of claim 108, selected from intrabuccal, intrapulmonary, respirable, nasal, inhalable, intracavitary, intraorgan, or slow release formulations.

144. The formulation of claim 143, wherein the carrier is selected from gaseous, solid or liquid carriers.

146. The aerosol formulation of claim 108, wherein which is selected from powders, sprays, solutions, suspensions or emulsions.

148. The aerosol formulation of claim 108, selected from aqueous or alcoholic solutions or suspensions, oily solutions or suspensions or oil-in-water or water-in-oil emulsions.

151. A capsule or cartridge, comprising the formulation of claim 143.

152. The aerosol formulation of claim 146, comprising a powdered spray or aerosol.

153. The formulation of claim 108, wherein the carrier comprises a

SERIAL NO: 08/093,972

hydrophobic carrier.

154. The formulation of claim 153, wherein the carrier comprises lipid vesicles and/or particles.

155. The formulation of claim 154, wherein the vesicles comprise liposomes and the particles comprise microcrystals.

156. The formulation of claim 155, wherein the vesicles comprise liposomes that comprise the nucleic acid.

158. (Twice Amended) The formulation of claim 143, which is an intrapulmonary, intracavitary or intraorgan liquid or powdered formulation of particle size about  $0.5\ \mu$  to  $10\ \mu$  or about  $10\ \mu$  to about  $500\ \mu$ .

159. (Twice Amended) The formulation of claim 143, which is a nasal formulation of particle size about  $10\ \mu$  to about  $500\ \mu$ .

161. The formulation of claim 143, in bulk, or in single or multiple unit dose form.

162. The formulation of claim 143, which is a respirable or inhalable formulation comprising a powdered or liquid aerosol of particle size about  $0.5\ \mu$  to about  $10\ \mu$ .

163. A cell, comprising the nucleic acid of claim 108.

164. A kit for diagnosis or treatment of diseases and conditions associated with hypersensitivity to and/or increased levels of, adenosine and/or bronchoconstriction and/or allergy(ies) and/or inflammation and/or asthma, comprising in separate containers [a]

the delivery device of claim 222;

a nucleic acid comprising at least one oligonucleotide (oligo) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, or alleviate bronchoconstriction, asthma or lung allergy(ies) and/or inflammation, the oligo being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, and/or increased levels of, adenosine, with bronchoconstriction, asthma, or lung allergy(ies) or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), their mixtures or their pharmaceutically or veterinarily

acceptable salts of the oligo(s); and

instructions for preparation of a respirable, inhalable, nasal, intrapulmonary, intraorgan, or intracavitary formulation of particle size about 0.5 to about 500  $\mu$  and for its use; and

optionally an agent selected from therapeutic or diagnostic agents other than the oligo, anti-oxidants, fillers, volatile oils, dispersants, anti-oxidants, flavoring agents, propellants, preservatives, solvents, buffering agents, RNA inactivating agents, agents that are internalized or up-taken by a cell, or coloring agents.

165. The kit of claim 164, wherein the delivery device comprises a nebulizer that delivers single metered doses of a powdered or liquid aerosol formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$  of the nucleic acid.

166. The kit of claim 164, wherein the device comprises an insufflator adapted for receiving and piercing or opening a capsule(s) or cartridge(s) producing a powdered or liquid aerosol; and the nucleic acid is provided separately in a pierceable or openable capsule(s) or cartridge(s) as a nasal, inhalable, respirable, intrapulmonary, intracavitary or intraorgan formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

167. The kit of claim 164, wherein the delivery device comprises a pressurized inhalator that delivers a powdered or liquid aerosol of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ ; and the nucleic acid is provided as a suspension, solution, emulsion or dry powder aerosol formulation of about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

168. (Twice Amended) The kit of claim 164, comprising the delivery device, a surfactant, the nucleic acid and a therapeutic agent selected from adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor antagonists other than the oligo(s), adenosine A<sub>2a</sub> receptor stimulants, anti-inflammatory agents, anti-histaminic agents, anti-allergic agents, anti-bacterial, anti-virals [vials], analgesics, kidney activity maintenance or restoration agents, anti-cancer agents, adenosine, blood pressure controlling agents, or diuretics.

169. The kit of claim 164, wherein the solvent is selected from organic solvents or organic solvents mixed with one or more co-solvents.

170. The kit of claim 164, wherein the device is adapted for receiving a



SERIAL NO: 08/093,972

capsule(s) or cartridge(s), and the nucleic acid is separately provided as an inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation in a capsule(s) or cartridge(s).

171. The kit of claim 164, further comprising in a separate container a propellant and pressurized means for delivery adapted for delivering a powdered or liquid aerosol, and instructions for loading into the delivery device [preparation and delivery of a composition comprising particles of about 0.05 to about 50  $\mu\text{m}$  in size of the nucleic acid] the nucleic acid as an inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ , and then joining the device with the propellant and the pressurized means.

172. The kit of claim 167, wherein the pressurized inhalator further comprises a propellant and means for delivery of the propellant, and delivers the nucleic acid as a liquid or powdered aerosol formulation of the nucleic acid.

173. An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to the airways of a subject an aerosol composition of particle size about 0.5  $\mu$  to about 500  $\mu$ , comprising a nucleic acid which comprises at least one oligonucleotide (oligo) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, or alleviate bronchoconstriction, asthma or lung allergy(ies) and/or inflammation, the oligo containing up to and including about 15% adenosine (A), [the oligo] and being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, and/or increased levels of, adenosine, with bronchoconstriction, asthma, or lung allergy(ies) and/or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), pharmaceutically and veterinarily acceptable salts of the oligo(s), mixtures of the oligo(s) or their salts.

175. (Twice Amended) The method of claim 173, wherein the hyper-responsiveness to, or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with sepsis, pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), renal damage or failure, ischemia, pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction,

emphysema, chronic obstructive pulmonary disease (COPD).

178. The method of claim 173, wherein the composition is administered intrapulmonarily, intraorgan, intracavitarily, intrabuccal, intranasally, by inhalation or into the subject's respiratory system.

179. The method of claim 173, wherein the oligo is effective to reduce hyper-responsiveness to adenosine, the amount of the adenosine receptor or the production or availability of adenosine, or to increase the degradation of the adenosine receptor mRNA.

180. The method of claim 178, wherein the oligo is administered directly into the subject's lung (s), intraorgan, intracavitarily, intrabuccal or intrapulmonarily.

181. The method of claim 178, wherein the composition is administered as powdered solid or liquid particles of the nucleic acid about 0.5 to about 10  $\mu$  in size.

183. The method of claim 181, wherein the composition is administered as powdered solid or liquid nucleic acid particles greater than about 10  $\mu$  in size.

184. The method of claim 173, wherein the composition further comprises a surfactant.

185. (Twice Amended) The method of claim [174] 173, wherein the hyper-responsiveness to, and/or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with bronchoconstriction of lung airways.

186. (Twice Amended) The method of claim 185, wherein the hyper-responsiveness to, or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with COPD, asthma, ARDS, RDS, CF or side effects of adenosine administration [or renal damage].

187. The method of claim 173, wherein the hyper-responsiveness to, or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with inflammation or an inflammatory disease.

188. (Twice Amended) The method of claim 173, wherein the composition further comprises a therapeutic agent selected from adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor inhibiting agents or adenosine A<sub>2</sub> receptor stimulating agents other than the nucleic acid(s), anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance or restoration agents or [gents] agents for the treatment of pulmonary

SERIAL NO: 08/093,972

vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema, or chronic obstructive pulmonary disease (COPD).

189. The method of claim 188, wherein the therapeutic agent is selected from anti-adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor agents or adenosine A<sub>2a</sub> receptor stimulating agents other than the nucleic acid(s).

191. (Twice Amended) The method of claim 184, wherein the surfactant is selected from surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, lamellar bodies, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene ethers, phenoxy polyethoxy alcohols, phosphatidyl choline esters and phosphatidyl ethers, palmitates, alcohols and tyloxapol, phospholipids, [neutral lipids,] fatty acids or surfactant-associated proteins, and C<sub>22</sub>H<sub>19</sub>C<sub>10</sub>.

192. The method of claim 173, wherein the subject is a mammal.

193. The method of claim 192, wherein the mammal is a human or a non-human mammal.

195. The method of claim 173, wherein the nucleic acid is administered in amount of about 0.005 to about 150 mg/kg body weight.

196. The method of claim 195, wherein the nucleic acid is administered in an amount of about 0.01 to about 75 mg/kg body weight.

197. The method of claim 196, wherein the nucleic acid is administered in an

amount of about 1 to about 50 mg/kg body weight.

198. The method of claim 173, which is a prophylactic or therapeutic method.

200. The method of claim 173, wherein the nucleic acid is obtained by

(a) selecting fragments of a target nucleic acid having at least 4 contiguous bases selected from the group consisting of G and C;

(b) obtaining a first oligo 4 to 60 nucleotide long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%; and

(c) obtaining a second oligo 4 to 60 nucleotide long comprising a sequence which is anti-sense to the selected fragment, the second oligo having an A base content of up to and including about 15%.

201. The method of claim 173, wherein the oligo consists of up to about 10% A.

202. The method of claim 201, wherein the oligo consists of up to about 5% A.

203. The method of claim 201, wherein the oligo consists of up to about 3% A.

204. The method of claim 203, wherein the oligo is A-free.

205. The method of claim 173, wherein the oligo is anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding an adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor and the composition further comprises a surfactant.

206. The method of claim 173, wherein if the oligo contains A, at least one A is substituted with a universal base selected from heteroaromatic bases which bind to a thymidine base but have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors, or heteroaromatic bases which have no activity or have an agonist activity at the adenosine A<sub>2a</sub> receptor.

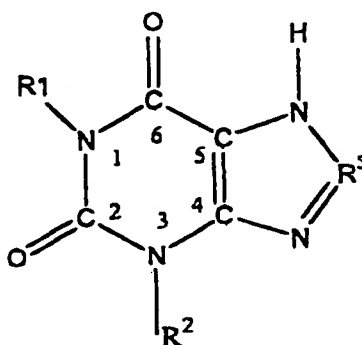
207. (Twice Amended) The method of claim 206, wherein substantially all As are substituted with universal bases selected from heteroaromatic bases which bind to a thymidine base but have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors, heteroaromatic bases which have no activity or have an agonist activity at the adenosine A<sub>2a</sub> receptor.

208. The method of claim 206, wherein the heteroaromatic bases are selected from pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH branched fused primary secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy,

cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo,  $\text{NH}_2$ , primary, secondary and tertiary amine, SH, SO,  $\text{SO}_2$ ,  $\text{SO}_3$ , cycloalkyl, heterocycloalkyl or heteroaryl.

209. The method of claim 208, wherein the pyrimidines are substituted at positions 1, 2, 3 and/or 4, and the purines are substituted at positions 1, 2, 3, 4, 7 and/or 8.

210. (Twice Amended) The method of claim 209, wherein the pyrimidines and purines are selected from theophylline, caffeine, dyphylline, etophylline, acephylline, piperazine, bamifylline, enprofylline or xantine having the chemical formula



wherein R<sup>1</sup> and R<sup>2</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxoalkoxy-aryl [and] or mono [and] or dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub> aryl.

211. The method of claim 206, wherein the universal base is selected from [the group consisting of] 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

212. The method of claim 173, further comprising methylating at least one cytosine vicinal to a guanosine into a methylated cytosine (<sup>m</sup>C) if a CpG dinucleotide is present in the oligo(s).

213. The method of claim 173, further comprising modifying or substituting at

least one mononucleotide of the anti-sense oligo(s) with methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues, or combinations thereof

214. (Amended) The method of claim 213, wherein substantially all mononucleotides are substituted and/or modified.

215. The method of claim 173, further comprising operatively linking the nucleic acid to an agent selected from agents that enhance cell internalization or up-take or cell targeting agents.

216. The method of claim 215, wherein the cell internalization or up-take enhancing agent is selected from transferrin, asialoglycoprotein or streptavidin.

217. The method of claim 215, wherein the cell targeting agent comprises a vector.

218. The method of claim 217, wherein the vector to which the agent is operatively linked comprises a prokaryotic or eukaryotic vector.

219. (Twice Amended) The method of claim 173, wherein the nucleic acid comprises an oligo sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 966 [1035], or SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO: 7 to SEQ ID NO: 966 [1035], wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotriester, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a

polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

220. (Amended) The method of claim 191, wherein the the surfactant is selected from polyoxy ethylene 23 lauryl ether (Brij 35<sup>®</sup>), t-octyl phenoxy polyethoxy ethanol (Triton X-100<sup>®</sup>), dipalmitoyl phosphatidyl choline (DPPC) and phosphatidyl glycerol (PG) (ALEC<sup>®</sup>), [colfoceryl-cetyl alcohol-tyloxapol or colfosceril palmitate, cetyl alcohol,] tyloxapol (Exosurf<sup>®</sup>), phospholipids, [neutral lipids,] fatty acids, surfactant-associated proteins (Survanta<sup>®</sup>) or C<sub>22</sub>H<sub>19</sub>C<sub>10</sub> (Atovaquone<sup>®</sup>).

221. The method of claim 173, wherein the hyper-responsiveness to, or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation is associated with asthma or a disease or condition associated with asthma.

222. A diagnostic or therapeutic device adapted for delivering a respirable, inhalable, nasal, intrapulmonary, intraorgan, or intracavitary formulation of particle size about 0.5  $\mu$  to about 500  $\mu$ , the formulation comprising a nucleic acid which comprises at least one oligonucleotide (oligo) effective for diagnosing or treating hyper-responsiveness to, or increased levels of, adenosine, or bronchoconstriction, asthma or lung allergy(ies) or inflammation, or a disease or condition associated with either of them, the oligo being anti-sense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness to, or increased levels of, adenosine, bronchoconstriction, asthma, or lung allergy(ies) or inflammation, or being anti-sense to the corresponding mRNA; the nucleic acid comprising one or more oligo(s), their mixtures, or their pharmaceutically or veterinarily acceptable salts.

223. The device of claim 222, comprising a nebulizer adapted for delivering single metered doses of the formulation as a powdered or liquid aerosol of particle size about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

224. The device of claim 222, which comprises an insufflator adapted for receiving and piercing or opening a capsule(s) or cartridge(s) and for producing a powdered or liquid aerosol of particle size about 0.5 $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ , and wherein the formulation is provided separately in a piercable or

openable capsule(s) or cartridge(s) as a nasal, inhalable, respirable, intrapulmonary, intracavitary or intraorgan formulation of particle size about  $0.5 \mu$  to about  $10 \mu$  or about  $10 \mu$  to about  $500 \mu$ .

225. The device of claim 222, which comprises a pressurized inhalator that delivers a powdered or liquid aerosol of particle size about  $0.5 \mu$  to about  $10 \mu$  or about  $10 \mu$  to about  $500 \mu$ ; and wherein the formulation comprises a suspension, solution, emulsion or dry powder aerosol formulation of the nucleic acid of particle size about  $0.05 \mu$  to about  $50 \mu$  or about  $10 \mu$  to about  $500 \mu$ .

226. The pressurized inhalator of claim 225, further comprising in a separate container a propellant and pressurized means for delivery, adapted for delivering a powdered or liquid aerosol, and instructions for loading into the delivery device the the inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation, and joining the device with the propellant and the pressurized delivery means.

227. The pressurized inhalator of claim 225, further comprising a propellant and propellant delivery means, wherein the pressurized inhalator delivers the formulation as a liquid or powdered aerosol.

228. The device of claim 222, which is adapted for receiving and piercing or opening a capsule(s) or cartridge(s), and the formulation is provided separately in a capsule(s) or cartridge(s).

229. (Amended) The kit of claim 164, wherein the oligo is antisense to the initiation codon, the coding region or the 5' or 3' region of a gene encoding a polypeptide selected from an adenosine  $A_1$  receptor, adenosine  $A_{2a}$  receptor, adenosine  $A_{2b}$  receptor, adenosine  $A_3$  receptor

[, IgE receptor  $\beta$ , Fc-epsilon receptor CD23 antigen, IgE receptor  $\alpha$  subunit, IgE receptor Fc  $\epsilon$  R, histidine decarboxylase, beta tryptase, tryptase-I, prostaglandin D synthase, cyclooxygenase-2, eosinophil cationic protein, eosinophil derived neurotoxin, eosinophil peroxidase, P selectin, endothelial monocyte activating factor (IL-3), interleukin-3 (IL-3), interleukin-5 (IL-5), interleukin-6 (IL-6), monocyte-derived neutrophil chemotactic factor, neutrophil elastase (medullasin), neutrophil oxidase factor, cathepsin G, defensin 1, defensin 3, macrophage inflammatory protein-1- $\alpha$ , muscarinic acetylcholine receptor HM1, muscarinic acetylcholine receptor HM3, fibronectin, interleukin-8 (IL-8), GM-



CSF, tumor necrosis factor  $\alpha$ , leukotriene C4 synthase or major basic protein].

230. (Amended) The kit of claim 229, for diagnosis or treatment of sepsis, pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), [renal damage or failure, ischemia,] pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, emphysema or chronic obstructive pulmonary disease (COPD).

231. (Amended) The kit [kiy] of claim 164, wherein the nucleic acid comprises an oligo sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 996 [1035], or SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO: 7 to SEQ ID NO: 996 [1035], wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotritioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol,olesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids.

Please add the following claims.

--232. The composition of claim 108, which comprises particle sizes of about 0.5  $\mu$  to about 10  $\mu$  or about 10  $\mu$  to about 500  $\mu$ .

233. The nucleic acid of claim 108, which is operatively linked to a vector.